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| 10/583,370 | 06/18/2007 | Michel Dreano | SCHIAFFONATI I | 8192 |

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| EXAMINER | |
|---|---|
| MERTZ, PREMA MARIA | |
| ART UNIT | PAPER NUMBER |
| 1646 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/583,370 | DREANO ET AL. | |
| | Examiner | Art Unit | |
| | Prema M. Mertz | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *19,21-23,25,28,31-36,40,41,43-45,48,50,53-55 and 57-62* is/are pending in the application.

4a) Of the above claim(s) *33-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/12/09 has been entered.

Claims 20, 24, 42, 47, and 49, have been canceled in the amendment filed 8/1/08, claims 37-39, and 46, have been canceled in the amendment filed 3/12/09 and claims 26-27, 29-30, and 51-52, have been canceled in the amendment filed 4/26/07.

Amended claims 19, 40-41, 55, previously presented claims 21-23, 25, 28, 31-32, 43-45, 48, 50, 53-54, and 57-62 are pending in the instant application.

Claims 33-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

2. Receipt of applicant's arguments and amendments filed on 3/12/2009 is acknowledged.

3. The following previous rejections and objections are withdrawn in light of applicants amendments filed on 3/12/2009:

(i) the rejection of claims 19, 21-23, 25, 28, 31-32, 40-41, 43-46, 48, 50, 53-55, 57-62, under 35 U.S.C. 112, second paragraph;

Applicant's arguments with respect to claims 23, 40, 48, and 61 have been considered but are moot in view of the new ground(s) of rejection.

(ii) the rejection of claims 19, 21-23, 25, 28, 31-32, 40-41, 43-46, 48, 50, 53-55, 57-62, under 35 U.S.C. 103(a) as being anticipated by Kovalovich et al. (2001).

4. Applicant's arguments filed on 3/12/09 have been fully considered and were persuasive in part. The issues remaining and new issues are stated below.

***Claim Rejections - 35 USC § 112, first paragraph, scope of enablement***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 19, 21-23, 25, 28, 31-32, 40-41, 43-46, 48, 50, 53-55, 57-62, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing proliferation of hepatocytes in CCl4 induced chemical cirrhosis, does not reasonably provide enablement for a method for treating liver cirrhosis as recited in claim 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth at pages 3-8 of the previous Office action of 5/1/2008 and pages 3-5 of the previous Office action of 9/12/2008.

Applicants argue that Applicants agree that there are different factors responsible for liver cirrhosis, however, the present claims are not directed to preventing liver cirrhosis but rather are directed to treating liver cirrhosis regardless of what factors caused the disease, as CC14 induced

chemical cirrhosis is an art accepted model for liver cirrhosis (as evidenced by the numerous references in the art to this animal model of liver cirrhosis) and for the study of treatment for liver cirrhosis in general, the presently claimed invention for treating liver cirrhosis is believed to be enabling to one of skill in the art. However, contrary to Applicants arguments, CCl4 induced chemical cirrhosis is a hepatotoxic agent induced cirrhosis unlike viral cirrhosis or autoimmune cirrhosis. Furthermore, Applicants have added dependent claims drawn specifically to "...cirrhosis is caused by hepatotoxic agents" which is a genus for the species "CCl4 induced chemical cirrhosis" CCl4 being a well-known hepatotoxin. In addition, Applicants argue that in contrast to the present invention, Kovalovich (2001) does not administer CC14 to induce liver cirrhosis but instead administers Jo-2 mAb in order to induce apoptosis. Therefore, Applicants are arguing on the record that CCl4 induced cirrhosis is disparate from Jo-2 mAb induced liver injury and hepatocyte apoptosis and that the factors causing liver cirrhosis are pertinent in the treatment of liver cirrhosis by IL-6. Therefore, contrary to Applicants arguments, the presently amended claims are not commensurate with the scope of the specification.

The declaration under 37 CFR 1.132 filed by Michel Dreano on 6/8/09 is insufficient to overcome the 35 USC 112, first paragraph, scope of enablement rejection of claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62 as set forth in the last Office action because: there is only support in the specification for enablement of the claim for a method of inducing proliferation of hepatocytes in CCl4 induced chemical cirrhosis. The declaration cites Jang et al., *Transplant Proceedings* 40:2700-2703 (2008) paper, and Weber et al., *Crit. Rev. Toxicol.* 33(2) :105-136 (2003), for the proposition that the CCl4 model is the most popular experimental

model for liver cirrhosis. However, there is absolutely no showing in the declaration that other than treatment of CCl4 induced liver cirrhosis by IL-6, liver cirrhosis caused by other agents can also be treated by administration of IL-6.

The declaration is non-persuasive because it reiterates Applicants' arguments regarding CCl4 induced chemical cirrhosis, which arguments have been addressed in the Office action filed on 9/12/2008 and 5/1/2008. Therefore, the declaration, does not overcome the 35 USC 112, first paragraph rejection of claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62. This declaration is not based on results or data relevant to all the defects recited in the claims and is of little probative value for the claimed method of treating liver cirrhosis by administering an effective dose of IL-6.

***Claim rejections-35 U.S.C. 112, second paragraph***

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 23, 40, 48, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 23, line 2, the phrase "includes" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Regarding claim 40, line 2, the phrase "including" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 48 and 61 are rejected as vague and indefinite insofar as they depend on the above rejected claim 40 for their limitations.

***Claim rejections-35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7a. Claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kovalovich et al. (2000).

Kovalovich et al discloses a method of treating liver injury caused by carbon tetrachloride treatment by administration of IL-6 at a dose of 1μg/g weight which protects against CCl4 induced liver injury in mice by reducing CCl4-induced acute and chronic liver injury (see abstract; see page 151, column 2, last paragraph; Figure 3b, page 154; page 158, column 1, first full paragraph). However, the reference does not specifically teach administering to the mice a dose of at IL-6 in the range of 0.1 to 10 μg/kg weight.

It would have been *prima facie* obvious to one having ordinary skill in the art to vary the dosage of the IL-6 to be administered in the method disclosed by Kovalovich such that it includes administering the IL-6 at a dose in the range of 0.1 to 10 μg/kg weight to obtain the desired effect of administering IL-6.

One of skill in the art of biological sciences would have been motivated to vary the dosage to obtain the therapeutically effective amount to treat cirrhosis because it is well known in the art that cytokines are toxic at high doses and it would be desirable to obtain a therapeutically effective amount of IL-6 at the lowest dosage possible. Using a dose-response curve is commonly practiced in the art of biological sciences. Study of the CCl4 effect by an IL-6 dose-response curve would have been obvious to one of skill in the art of biological sciences. It would have been obvious to the skilled artisan to vary the dosage and the results achieved would

have been expected. Therefore, the Kovalovich reference renders obvious claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62.

The declaration under 37 CFR 1.132 filed by Michel Dreano on 6/8/09 is insufficient to overcome the 35 USC 103(a) rejection of claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62 based upon the Kovalovich reference as set forth in the last Office action because:

The declaration sates that it provides references to support the position that compounds exhibiting beneficial effects when administered before the onset of a pathological situation (pre-treatment) would NOT be expected to be effective when administered therapeutically to treat the pathological situation. The declaration states that the Gardiner et al., *Br. J. Pharmacol.* 128:1778-1782 (1999), reference reported that, using a rat model of vasodilation induced by infusion of liposaccharides, pre- or post-treatments with glibenclamide (potassium-ATP channel antagonist) result in different biological effects. Whereas pre-treatment abolished the initial hypotension but not renal vasodilation, post-treatment instead led to a significant increase in mean arterial blood pressure and reduction in renal conductance. Similarly, the declaration states that in the second example from Hom et al., J. *Pharmacol. Exp. Therap.* 272:452-459 (1995), significant differences between pre- and post-treatments were observed using a LPS-induced hypotension and vascular hypo-reactivity rat model. Pre-treatment with dexamethasone significantly attenuated LPS-induced norepinephrine hypo-responsiveness, while post-treatment had no effect. In parallel experiments, the authors showed that N-monomethyl-L-arginine (LNMMA) induced hypo-responsiveness after both pre- or post-treatments.

Firstly, in both references LPS is the endotoxin being administered. By using the LPS comparison, Applicants are comparing apples to oranges. Just as Applicants are arguing that the administration of Jo-2 mAb would induce apoptosis rather than liver cirrhosis induced by CCl4 treatment, the effects of LPS pre-treatment or post-treatment has no bearing on IL-6 pre-treatment or post-treatment. Furthermore, with respect to the instant Kovalovich reference, Applicants have not shown that IL-6 pre-treatment followed by CCl4 treatment would not produce the same results as post-treatment with IL-6. Therefore, the declaration is an opinion since no results have been submitted.

The declaration also states that the results reported in Di Marvo et al., *J. Neuroimmunol.* 116:168-177 (2001), clearly show that daily s.c. administration of IL-6 in rats starting at the peak of experimental allergic encephalomyelitis significantly reduced the clinical disease course (i.e., reduced the number and diminished the severity of relapses), while an early IL-6 treatment before the onset of clinical signs did not alter the progression of the disease. However, contrary to the assertions in the declaration, as argued by the Examiner previously, Applicants have not shown that IL-6 pre-treatment followed by CCl4 treatment would not produce the same results as post-treatment with IL-6. Furthermore, contrary to the arguments in the declaration, there is no limitation about the unexpected results obtained by the IL-6 post-treatment effect being claimed.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. Therefore, contrary to the assertions in the declaration and in Applicants arguments, the reference renders obvious claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, and 57-62.

7b. Claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62, are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/02552 (1999).

The reference discloses a method of treating liver injury caused by carbon tetrachloride treatment by administration of IL-6R/IL-6 chimera at a dose of 2-3 microgram 1 hour before and 4 hours after CCl4 protects against CCl4 induced liver injury in mice by reducing CCl4-induced acute and chronic liver injury and reducing mortality (see abstract; see page 5, lines 1-14, page 27, lines 3-10 and Example 8, pages 39-40). However, the reference does not specifically teach administering to the mice a dose of IL-6 chimera in the range of 0.1 to 10 μg/kg weight.

It would have been *prima facie* obvious to one having ordinary skill in the art to vary the dosage of the IL-6 chimera to be administered in the method disclosed by the reference such that it includes administering the IL-6 chimera at a dose in the range of 0.1 to 10 μg/kg weight to obtain the desired effect of administering IL-6.

One of skill in the art of biological sciences would have been motivated to vary the dosage to obtain the therapeutically effective amount to treat cirrhosis because it is well known in the art that cytokines are toxic at high doses and it would be desirable to obtain a therapeutically effective amount of IL-6 at the lowest dosage possible. Using a dose-response curve is commonly practiced in the art of biological sciences. Study of the CCl4 effect by an IL-6 dose-response curve would have been obvious to one of skill in the art of biological sciences. It would have been obvious to the skilled artisan to vary the dosage and the results achieved would have been expected. Therefore, the reference renders obvious claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, 57-62.

***Conclusion***

No claim is allowed.

Claims 19, 21-23, 25, 28, 31-32, 40-41, 43-45, 48, 50, 53-55, and 57-62, are rejected.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Prema Mertz whose telephone number is (571) 272-0876. The examiner can normally be reached on Monday-Friday from 7:00AM to 3:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835.

Official papers filed by fax should be directed to (571) 273-8300. Faxed draft or informal communications with the examiner should be directed to (571) 273-0876.

Information regarding the status of an application may be obtained from the Patent application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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